Rare case of obstetric cholestasis presenting in the first trimester following in vitro fertilisation

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SUMMARY

Intrahepatic cholestasis of pregnancy (ICP) generally presents in the third trimester with pruritus without a rash, characterised by elevated bile acids, with or without transaminitis and hyperbilirubinaemia. Risk factors include a family history of cholestasis, South Asian ethnicity, multifetal gestation, in vitro fertilisation (IVF) and history of hepatitis or biliary disorders.

IVF involves the use of high dose gonadotropin stimulation and human chorionic gonadotropin trigger. High doses of progesterone supplementation are additionally given after embryo transfer. The increase in oestrogen and progesterone levels early on in the pregnancy is a possible explanation for the development of ICP in IVF pregnancies at earlier gestations.

We present a rare case of iatrogenic ICP presenting in the first trimester in a pregnancy conceived by IVF. Unlike other cases reported, our patient did not have recurrence of ICP in the third trimester, and also had no history of ICP in her first pregnancy.

BACKGROUND

Intrahepatic cholestasis of pregnancy (ICP) is a hepatic disorder typically presenting in the third trimester with pruritus, typically on the palms and soles, without a rash, characterised by elevated bile acids, with or without transaminitis and hyperbilirubinaemia.

The diagnosis is made after exclusion of other diseases causing cholestasis including gallstones, viral and autoimmune hepatitis. It has a genetic and ethnic predisposition, being more common in women with a family history of cholestasis or of South Asian ethnicity. Other risk factors include multifetal gestation, in vitro fertilisation (IVF), and history of hepatitis or biliary disorders.[1] The pathogenesis of ICP has been linked to genetic mutations in biliary transport proteins, and high circulating oestrogen and progesterone levels, such as that found in multiple gestations and with increasing gestation,[1] which impairs bile acid homoeostasis mechanisms by repressing the expression of the bile salt export pump[2] or by upregulating the pregnane X receptor signalling pathway.[3]

Although uncommon, ICP has clinically significant implications on pregnancy outcomes as higher bile acid levels are associated with increased risk of stillbirth, meconium stained amniotic fluid, fetal distress, preterm delivery, caesarean section rates and neonatal intensive care unit stay.[4] It also increases risk of maternal haemorrhage, development of liver and biliary disorders and recurrence in future pregnancies.[5 6]

The incidence of ICP has been found to be higher in pregnancies conceived by IVF compared with those conceived spontaneously,[7 8] with occasional onset at earlier gestations, more intense pruritus, and higher rates of neonatal asphyxia and premature delivery.[9] Adverse fetal outcomes including low birth weight, fetal morbidity and mortality were also found in one study to be more common in early-onset ICP less than 28 weeks gestation.[9] The higher levels of bile acids in IVF pregnancies is postulated to be due to the higher rates of multiple pregnancies and hormonal treatment,[10] as manifested by higher maternal serum oestradiol levels at 4–8 weeks gestation in pregnancies conceived by IVF.[11]

We present a rare case of iatrogenic ICP presenting in the first trimester in a pregnancy conceived by IVF, which subsequently resolved and did not recur in the third trimester. To the best of our knowledge, this is the first case presented in the literature of an early-onset ICP following an IVF pregnancy, with no recurrence in the third trimester.

CASE PRESENTATION

Our patient was a gravida 2 para 1 woman of Indian ethnicity in her late 20s, with no significant medical or family history of liver disorders.

Her first pregnancy in 2017 was conceived by IVF and intracytoplasmic sperm injection (ICSI) with transfer of a single day two embryo, which resulted in a successful pregnancy. She received a total of 9 days of stimulation with the recombinant follicle stimulating hormone (FSH) Follitropin (Gonal-F) at a dose of 150 IU per day, concurrently with the gonadotropin releasing hormone antagonist ganirelix (Orgalutron) for 250 µg/day. A total of 11 eggs were collected and 2 were successfully fertilised and cleaved. Her luteal support regime consisted of progesterone (Crinone) 8% gel two times a day for 17 days, starting from the date of embryo transfer, followed by oral progesterone (dydrogesterone) 10 mg two times a day for 3 months. Her antenatal course was uneventful with no ICP, gestational diabetes or other complications, other than some nausea and vomiting for up to the fifth month of pregnancy, which was managed with promethazine and required one admission for intravenous fluid hydration. She delivered a healthy term baby girl by normal vaginal delivery.

In February 2019, the patient underwent another cycle of IVF and ICSI that was unsuccessful.

The index pregnancy was conceived by IVF and ICSI in October 2019 in a different IVF centre using a differing regime. She received a total of 10 days of Follitropin (Gonal-F)—300 IU for the first to fourth days, 450 IU for the fifth and eighth days and 375 IU for the sixth, seventh, ninth and tenth days. The gonadotropin releasing hormone antagonist agent used was cetrorelix (Cetrotide), given at a dose of 0.25 mg

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was from the fifth to tenth days of stimulation. She had a recombinant human chorionic gonadotropin (Ovidrel) trigger on the 11th day. Oocyte pickup was performed 2 days after the trigger. There were a total of 10 follicles present, total 7 mature oocytes recovered and fertilisation was done by ICSI. Six oocytes were fertilised and six embryos cleaved. Two embryos were transferred at the day two stage, resulting in a successful pregnancy and given an estimated date of delivery of 23 June 2020. After the embryo transfer, she was started on oestrogen supplementation in the form of oral Progynova 2 mg and vaginal progesterone in the form of Utrogestan 200 mg three times a day for luteal support. She developed vaginal spotting 15 days after the embryo transfer and was started on additional oral dydrogesterone 10 mg two times a day.

The patient first presented with severe nausea at 7 weeks gestation, controlled with oral antiemetics. At 8 weeks gestation, she developed intense pruritus, worse at night, affecting her palms and soles. At 9 weeks and 6 days of gestation, serum bile acids were elevated at 18.3 µmol/L (normal range 1–6 µmol/L) with transaminitis. Serum alanine transaminase (ALT) level was 328 U/L (normal range 0–55 U/L) and aspartate transaminase (AST) level was 110 U/L (normal range 5–34 U/L). Viral and autoimmune hepatitis screen were negative. At 10+3 weeks gestation, she was started on ursodeoxycholic acid (UDCA) 500 mg two times a day, her oestrogen supplementation stopped, and luteal support progesterone pessary was reduced from three times a day to two times a day. Oral progesterone supplementation was stopped at this point, but restarted 4 days later at 11+0 weeks when she developed vaginal spotting again. She continued the same dose of oral progesterone supplementation until 17 weeks of gestation. Repeat bloods at 11+5 weeks of gestation found bile acids found bile acids to be within normal range at 5.8 µmol/L and transaminases showing a downward trend, with ALT level of 49 U/L and AST level of 16 U/L. Her UDCA was stopped at 14+1 weeks of gestation. At this point her bile acid level was 2.3 µmol/L and transaminitis had resolved.

INVESTIGATIONS

The relevant investigations have already been detailed in the Case presentation section.

DIFFERENTIAL DIAGNOSIS

ICP is a diagnosis of exclusion and the presentation in our patient was unusual due to its occurrence in the first trimester. Other causes of hepatitis and cholestasis were considered and excluded by relevant investigations, including those for viral and autoimmune hepatitis.

TREATMENT

The treatment of the condition has been detailed in the Case presentation section.

OUTCOME AND FOLLOW-UP

She was monitored closely throughout the rest of the pregnancy for any clinical features of recurrence of cholestasis. In the second trimester of pregnancy, a baseline liver function test at 20 weeks of gestation was normal. In the third trimester, although she developed itch at 33+1 weeks and 36+1 weeks of gestation, liver function tests performed on both occasions found transaminase levels within the normal ranges. Serum bile acid levels were not repeated in view of the normal transaminase levels.

At 39+1 weeks of gestation, she presented in spontaneous term labour and had an uneventful normal vaginal delivery. She delivered a healthy baby girl of birth weight 3090 g and Apgar scores of 9 and 9 and 1 min and 5 min, respectively. The patient was discharged well and stable on the second postpartum day.

DISCUSSION

The IVF cycle involves the use of high dose gonadotropin stimulation and human chorionic gonadotropin trigger, with the correspondent increase in oestrogen levels, as manifested by higher maternal serum oestradiol levels at 4–8 weeks gestation in pregnancies conceived by IVF.[11] High doses of progesterone supplementation are additionally used for the luteal support phase after embryo transfer. These factors increase the circulating oestrogen and progesterone levels early on in the pregnancy and are a possible explanation for impaired bile acid homoeostasis and development of ICP in the first trimester of some IVF pregnancies. In addition, the higher rates of multiple pregnancies in IVF pregnancies is another postulated explanation for the higher levels of bile acids in IVF pregnancies due to the resultant increase in oestrogen levels.[10]

As discussed earlier, not only has the incidence of ICP has been found to be higher in pregnancies conceived by IVF compared with those conceived spontaneously,[7 8] but ICP in IVF pregnancies occasionally present at earlier gestations and with more intense pruritus. There are also higher rates of neonatal asphyxia and premature delivery.[9] Additionally, adverse fetal outcomes including low birth weight, fetal morbidity and mortality were also found in one study to be more common in early-onset ICP less than 28 weeks gestation.[9]

This is one of few cases presented in the literature of early onset ICP following IVF and ovarian stimulation.[12 13] While two of the other cases reported had recurrence of ICP in the third trimester following normalisation of bile acids in the second trimester,[14] our case is unique because she did not have recurrence of ICP in the third trimester. She also did not have any history of ICP in her first pregnancy, which was conceived by IVF although using a different regime. In the patient's first IVF cycle, she received a lower dose of recombinant FSH (150 IU daily compared with 300–450 IU in the index IVF cycle), and a less intensive luteal support regime (consisting of vaginal progesterone two times a day and oral dydrogesterone, compared with both oral progynova, vaginal progesterone three times a day and oral dydrogesterone in the index IVF cycle). The higher exposure to exogenous hormones in the index IVF cycle may explain the occurrence of early onset ICP, whereas she had no history of ICP in the pregnancy conceived by the first IVF cycle. The cessation of oestrogen and reduction of progesterone supplementation most likely led to the resolution of symptoms and normalisation of bile acids at the end of the first trimester.

Patient's perspective

IVF can be a daunting, physically and emotionally stressful journey. During this process I urge women to trust their instincts as they know their body best, voice their concerns, and make sure their concerns are heard. As this condition is rare, our incredible doctors had some understandable doubts about it initially. I hope that this publishing will better equip doctors, and thus patients, to recognise the condition sooner and thus treat it as early as possible. If this stressful journey can be made any less stressful, I believe it would make all the difference.

Contributors KK summarised the case records and wrote the paper. MM managed the case presented, and both MM and RK supervised and contributed to writing

Learning points

- This is an atypical presentation of iatrogenic intrahepatic cholestasis of pregnancy (ICP) resulting from exogenous in vitro fertilisation (IVF) hormonal stimulation, presenting in the first trimester, with resolution following removal of the hormonal triggers, and no recurrence in the third trimester.
- It illustrates the role of high circulating oestrogen and progesterone levels in the pathogenesis of ICP, and highlights the need for high index of suspicion for the development of ICP in IVF pregnancies at earlier gestations.
- Prompt recognition and treatment of ICP with removal of hormonal triggers and ursodeoxycholic acid is crucial for symptomatic relief and prevention of adverse fetal and neonatal outcomes.

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